REVIEW ARTICLE

A C G publications

Rec. Nat. Prod. X:X (2022) XX-XX

records of natural products

A Review on Medical Plants of Genus *Siegesbeckia*: Phytochemical and Pharmacological Studies

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(Received January 26, 2022; Revised March 21, 2022; Accepted March 23, 2022)

Abstract: Genus *Siegesbeckia* has been utilized as herbal medicine for treating arthritis, stroke, rash and other diseases for hundreds of years in East Asia. Modern pharmacological researches demonstrated the species of genus *Siegesbeckia* contains numerous naturally occurring active compounds. Till now, 250 compounds have been separated from *Siegesbeckia* species, namely 128 diterpenoids, 71 sesquiterpenoids, 14 flavonoids and 37 other compounds. A number of studies showed *Siegesbeckia* extracts or constituents possessed various therapeutic activities, including anti-inflammation, analgesia, anti-cancer and so on. Some of them have a bright prospect in naturally occurring drug discovery.The information provided by this review is expected to be beneficial for further phytochemical and pharmacological studies of the genus *Siegesbeckia*.

Keywords: *Siegesbeckia*; kirenol; diterpenoid; anti-inflammation; sesquitepenoid.

1. Introduction

The genus *Siegesbeckia*, as a part of Asteraceae family, consists of 12 species which mainly existed in tropical, subtropical and temperate zones. Some of them have been employed as medicinal herbs in China, Korea and other countries from ancient times. In about 659 AD, the dried aboveground parts of three species, namely *S. orientalis*, *S. pubescens* and *S. glabrescens*, were first documented in Xin Xiu Ben Cao (The newly-revised materia medica) in ancient China by the name of "Xi xian cao" for treatment of arthritis, stroke, rash, edema and so on. Besides, *S. pubescens* is also used for the treatment of hypertension, headache and vertigo disease as "Huiryeom" in Korea [1]. Recent pharmacology researches reported that plants of genus *Siegesbeckia* exhibited significant therapeutic effects on anti-inflammation, analgesia, anti-thrombosis, anti-cancer and other diseases.

In recent years, the genus *Siegesbeckia* attracted large attention of pharmaceutical scientists. This review summarizes the phytochemical profile, pharmacological value and proposed further perspectives on genus *Siegesbeckia* based on the literature over the past decades.

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The article was published by ACG Publications
http://www.acgpubs.org/journal/records-of-natural-products Month-Month 202x EISSN:1307-6167
DOI: http://doi.org/10.25135/rnp.317.2201.2332
Available online: April 12, 2022

2. Chemical Constituents

To date, 250 compounds with various chemical structures have been identified from genus *Siegesbeckia*, which include *ent*-kaurane and *ent*-pimarane diterpenoids, sesquiterpenoids, flavonoids and other compounds. The structures and sources were depicted in Table 1-4 and Figure 1-5, respectively. Amongst, *ent*-kaurane and *ent*-pimarane diterpenoids are often considered as the active compounds of this genus.

2.1. Diterpenoids

Diterpenoid, a terpene with a 20-carbon skeleton, is derived from the assembly of four isoprene units. Diterpenoid is one of the most prevalent classes of genus *Siegesbeckia*. A total of 128 diterpenes have been identified from *S. orientalis*, *S. pubescens* and*S. glabrescens.* They are structurally categorized into four groups, namely *ent*-pimarane diterpenoids, *ent*-kaurane diterpenoids, chain diterpenes and*ent*-strobane diterpenoids, respectively.

The *ent*-pimarane diterpenoid is the most common diterpenoids in genus *Siegesbeckia*. Totally 83 of them (**1**-**83**) have been identified up to date. The *ent*-pimarane diterpenoid is a tricyclic diterpene with *β*-CH_3 at C-17, *α*-CH_3 at C-19 and C-20, and *β*-H at C-5, C-8 and C-9. A small number of *ent*-pimarane diterpenoids from genus *Siegesbeckia* contains an epoxy group between C-14 and C-16 (**42**, **43**, **58**, **59**) or C-12 and C-16 (**44**, **45**). Furthermore, four *ent*-pimarane diterpenoids contain an acetonide group at C-15 and C-16 (**33**-**35**, **40**). The glycosyl group usually appears at C-18 (**8**, **9**, **12**, **21**, **22**, **27**, **33**), C-3 (**2**, **16**, **17**, **20**, **32**, **35**, **36**, **39**), C-15 (**2**), C-16 (**30**) and C-2 (**7**). Amongst, the neodarutoside (**2**) is the only disaccharide glycoside of *ent*-pimarane diterpenoid from genus *Siegesbeckia*. Recently, three diterpenoid dimers (**81**-**83**) were isolated and identified from *S.GS. glabrescens* [2].

The *ent*-kaurane diterpenoid is another prevalent diterpenoid from genus *Siegesbeckia* with a tetracyclic structure. A total of 33*ent*-kaurane diterpenoids (**84**-**116**) have been identified from this genus. Except of common substituted groups such as hydroxyl, carboxyl, and methoxyl groups, isobutyryloxy group appeared at C-17 of *ent*-kaurane diterpenoid (**109)**and C-18 of compound (**92)**. Furthermore, compounds (**111**, **112**) contain an acetonide group between C-16 and C-17. Besides, compounds (**113**-**116**) are the only four glucopyranosides of *ent*-kaurane diterpenoids from genus *Siegesbeckia*.As for other diterpenoids, only ninechain diterpenoids (**117**-**125**) andthree*ent*-strobane diterpenoids (**126**-**128**) were reported from genus *Siegesbeckia* till now.

Table 1. *ent*-pimarane diterpenoids isolated from genus *Siegesbeckia*

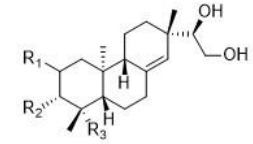
No.	Compounds	Plants	Ref.	No.	Compounds	Plants	Ref.
1	darutigenol	*S. orientalis*	[3]	**43**	*ent*-14*β*,16-epoxy-8-pimar-ene-3*β*,15*α*-diol	*S. orientalis*	[4]
2	neodarutoside	*S. glabrescens*	[5]	**44**	*ent*-12*α*,16-epoxy-2*β*,15*α*,19-trihydroxypimar-8(14)-ene	*S. orientalis*	[6]
3	12-hydroxykirenol	*S. pubescens*	[7]	**45**	*ent*-12*α*,16-epoxy-2*β*,15*α*,19-trihydroxypimar-8-ene	*S. orientalis*	[6]
4	orientalin A	*S. orientalis*	[8]	**46**	*ent*-16-nor-3-oxo-pimar-8(14)-en-15-al	*S. pubescens*	[9]
5	orientalin B	*S. orientalis*	[8]	**47**	19-hydroxy-15-devinyl-*ent*-pimar-8,11,13-triene-2,7-dione	*S. pubescens*	[10]
6	kirenol	*S. orientalis*	[8]	**48**	2*β*,19-dihydroxy-15-devinyl-*ent*-pimar-8,11,13-triene	*S. pubescens*	[10]

Table 1 continued..

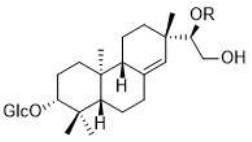
7	*ent*-2*α*,15,16-trihydroxypimar-8(14)-en-2-*O*-*β*-D-glucopyranoside	*S. pubescens*	[11]	**49**	*ent*-3*β*,15*R*,16-trihydroxypimar-8(14)-diene	*S. pubescens*	[10]
8	*ent*-15,16,19-trihydroxypimar-8(14)-en-19-*O*-*β*-D-glucopyranoside	*S. pubescens*	[11]	**50**	*ent*-2*α*,15*R*,16,19-tetrahydroxy pimar-8(14)-ene	*S. pubescens*	[10]
9	*β*-D-glucopyranosyl-*ent*-15,16-dihydroxypimar-8(14)-en-19-oiclate	*S. pubescens*	[11]	**51**	*ent*-2*β*,15,16,19-tetrahydroxy pimar-8(14)-ene	*S. pubescens*	[10]
10	*ent*-2*β*,15,16-trihydroxy-pimar-8(14)-ene	*S. orientalis*	[12]	**52**	*ent*-2*α*,15,16,18-tetrahydroxy pimar-8(14)-ene	*S. pubescens*	[10]
11	*ent*-2*α*,15,16,19-tetrahydroxy pimar-8(14)-ene	*S. orientalis*	[6]	**53**	*ent*-15,16-dihydroxy-18-norpimar-8(14)-en-3-one	*S. pubescens*	[10]
12	*ent*-2*β*,15,16,19-tetrahydroxypimar-8(14)-en-19-*O*-*β*-glucopyranoside	*S. orientalis*	[6]	**54**	*ent*-1*β*,3*β*,15,16-tetrahydroxy pimar-8(14)-ene	*S. pubescens*	[10]
13	7*β*-hydroxydarutigenol	*S. orientalis*	[4]	**55**	*ent*-3*β*,15,16-trihydroxy pimar-6,8(14)-diene	*S. pubescens*	[10]
14	9*β*-hydroxydarutigenol	*S. orientalis*	[4]	**56**	*ent*-2*α*,15,16,19-tetrahydroxy pimar-6,8(14)-diene	*S. pubescens*	[10]
15	16-*O*-acetyldarutigenol	*S. orientalis*	[4]	**57**	*ent*-15,16-dihydroxypimar-1,8(14)-dien-3-one	*S. pubescens*	[10]
16	15,16-di-*O*-acetyldarutoside	*S. orientalis*	[4]	**58**	14*β*,16-epoxy-*ent*-3*β*,15*α*,19-trihydroxypimar-7-ene	*S. pubescens*	[10]
17	16-*O*-acetyldarutoside	*S. orientalis*	[4]	**59**	14*β*,16-epoxy-*ent*-3*α*,15*α*,19-trihydroxypimar-7-ene	*S. pubescens*	[10]
18	darutoside	*S. orientalis*	[4]	**60**	*ent*-2*β*,15*R*,16-trihydroxy-19-oxo pimar-8(14)-ene	*S. pubescens*	[13]
19	*ent*-2*β*,15,16-trihydroxypimar-8(14)-en-19-oic acid	*S. pubescens*	[14]	**61**	siegesbeckia A	*S. glabrescens*	[15]
20	hythiemoside B	*S. orientalis*	[16]	**62**	siegesbeckia B	*S. glabrescens*	[15]
21	*ent*-(15*R*),16,19-trihydroxypimar-8(14)-ene 19-*O*-*β*-D-glucopyranoside	*S. orientalis*	[16]	**63**	siegesbeckia C	*S. glabrescens*	[15]
22	*ent*-15-methylene-2*α*,16,19-trihydroxy-pimar-8(14)-ene-19-*O*-*β*-D-glucopyranoside	*S. pubescens*	[17]	**64**	siegesbeckia D	*S. glabrescens*	[15]
23	*ent*-2*α*,3*β*,15,16,19-pentahydroxypimar-8(14)-ene	*S. pubescens*	[10]	**65**	siegesbeckia E	*S. glabrescens*	[15]
24	*ent*-2*α*,7*α*,15,16,19-pentahydroxypimar-8(14)-ene	*S. pubescens*	[10]	**66**	siegesbeckia F	*S. glabrescens*	[15]
25	*ent*-2*α*,7*β*,15,16,19-pentahydroxypimar-8(14)-ene	*S. pubescens*	[10]	**67**	siegesbeckia G	*S. glabrescens*	[15]
26	2-keto-16-acetyloxykirenol	*S. pubescens*	[7]	**68**	siegesbeckia H	*S. glabrescens*	[15]
27	*ent*-2-oxo-15,16,19-trihydroxy pimar-8(14)-en-19-*O*-*β*-D-glucopyranoside	*S. pubescens*	[11]	**69**	siegesbeckia I	*S. glabrescens*	[15]
28	15,16-dihydroxy-2-oxo-pimar-8(14)-ene	*S. orientalis*	[12]	**70**	sigesbeckia J	*S. glabrescens*	[18]

Table 1 continued..

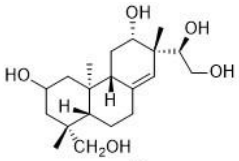
29	15,16,18-trihydroxy-2-oxo-pimar-8(14)-ene	*S. orientalis*	[12]	**71**	sigesbeckia K	*S. glabrescens*	[19]
30	*ent*-2-oxo-15,16-dihydroxy pimar-8(14)-en-16-*O*-*β*-glucopyranoside	*S. orientalis*	[6]	**72**	sigesbeckia L	*S. glabrescens*	[19]
31	*ent*-2-oxo-15,16,19-trihydroxy pimar-8(14)-ene	*S. orientalis*	[6]	**73**	*ent*-16-nor-2-oxopimar-8(14)-ene-15,19-dial	*S. pubescens*	[20]
32	*ent*-2-oxo-3*β*,15,16-trihydroxy pimar-8(14)-en-3-*O*-*β*-glucopyranoside	*S. orientalis*	[6]	**74**	*ent*-16-nor-2*α*,19-dihydroxypimar-8-en-15-al	*S. pubescens*	[20]
33	*ent*-2-oxo-15,16,19-trihydroxy pimar-8(14)-en-19-*O*-*β*-D-glucopyranoside-15,16-acetonide	*S. pubescens*	[11]	**75**	3-*O*-acetyldarutigenol	*S. pubescens*	[20]
34	*ent*-3*α*,15,16-trihydroxypimar-8(14)-en-15,16–acetonide	*S. pubescens*	[14]	**76**	19-*O*-acetylkirenol	*S. pubescens*	[20]
35	*ent*-3*α*,15,16-trihydroxypimar-8(14)-en-3*α*-*O*-*β*-glucopyranoside-15,16-acetonide	*S. pubescens*	[14]	**77**	*ent*-16-nor-3*β*,15-dihydroxy pimar-8(14)-ene	*S. pubescens*	[20]
36	*ent*-16-acetoxy-3*α*,15-dihydroxy-14*α*-hydroperoxypimar-7-en-3*α*-*O*-*β*-gluco-pyranoside	*S. pubescens*	[14]	**78**	1*R*,3*R*,15*R*,16-tetrahydroxy-*ent*-pimar-8(14)-ene	*S. pubescens*	[21]
37	*ent*-3*α*,7*β*,15,16-tetrahydroxypimar-8(14)-ene	*S. pubescens*	[14]	**79**	1*R*,3*R*,15*R*,16-tetrahydroxy-*ent*-pimar-8(14)-ene	*S. pubescens*	[21]
38	*ent*-3*α*,15,16,19-tetrahydroxypimar-8(14)-ene	*S. pubescens*	[14]	**80**	3*β*,15*R*,16-trihydroxy-*ent*-pimar-8(14)-ene	*S. pubescens*	[21]
39	*ent*-16-acetoxy-15-hydroxypimar-8 (14)-en-3*α*-*O*-*β*-glucopyranoside	*S. pubescens*	[14]	**81**	glabreside A	*S. glabrescens*	[2]
40	isopropylidenkirenol	*S. pubescens*	[14]	**82**	glabreside B	*S. glabrescens*	[2]
41	*ent*-15-oxo-2*β*,16,19-trihydroxypimar-8(14)-ene	*S. orientalis*	[6]	**83**	glabreside C	*S. glabrescens*	[2]
42	*ent*-14*β*,16-epoxy-8-pimar-ene-2*α*,15*α*,19-triol	*S. orientalis*	[4]				



1 R_1 = H, R_2 = OH, R_3 = CH_3
6 R_1 = OH, R_2 = H, R_3 = CH_2OH
7 R_1 = OGlc, R_2 = H, R_3 = CH_3
8 R_1 = H, R_2 = H, R_3 = CH_2OGlc
9 R_1 = H, R_2 = H, R_3 = $CH_2COOGlc$
10 R_1 = β-OH, R_2 = H, R_3 = CH_3
11 R_1 = OH, R_2 = H, R_3 = CH_2OH
12 R_1 = OH, R_2 = H, R_3 = CH_2OGlc
19 R_1 = OH, R_2 = H, R_3 = COOH
21 R_1 = H, R_2 = H, R_3 = OGlc



2 R=Glc
18 R=H



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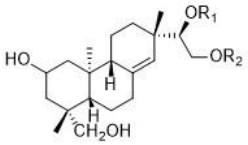
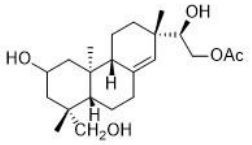


4 R_1 = Ac, R_2 = H
5 R_1 = H, R_2 = Ac



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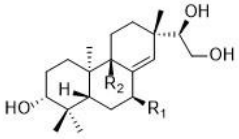
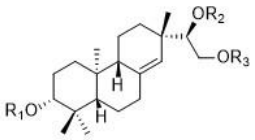
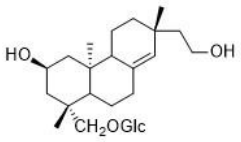


13 R_1 = OH, R_2 = H
14 R_1 = H, R_2 = OH



15 R_1 = H, R_2 = H, R_3 = Ac
16 R_1 = Glc, R_2 = Ac, R_3 = Ac
17 R_1 = Glc, R_2 = H, R_3 = Ac
20 R_1 = Glc, R_2 = Ac, R_3 = H



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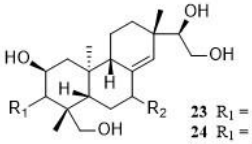
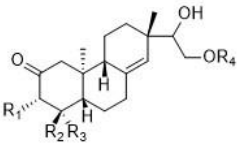
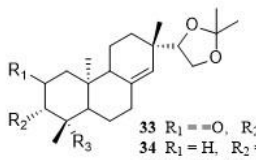


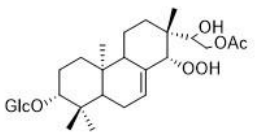
23 R_1 = α-OH, R_2 = H
24 R_1 = H, R_2 = β-OH
25 R_1 = H, R_2 = α-OH



26 R_1 = H, R_2 = CH_3, R_3 = CH_2OH, R_4 = Ac
27 R_1 = H, R_2 = CH_3, R_3 = CH_2OGlc, R_4 = H
28 R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = H
29 R_1 = H, R_2 = CH_2OH, R_3 = CH_3, R_4 = H
30 R_1 = H, R_2 = CH_3, R_3 = CH_3, R_4 = Glc
31 R_1 = H, R_2 = CH_3, R_3 = CH_2OH, R_4 = H
32 R_1 = OGlc, R_2 = CH_3, R_3 = CH_3, R_4 = H



33 R_1 = =O, R_2 = H, R_3 = CH_2OGlc
34 R_1 = H, R_2 = OH, R_3 = CH_3
35 R_1 = H, R_2 = OGlc, R_3 = CH_3
40 R_1 = OH, R_2 = H, R_3 = CH_2OH



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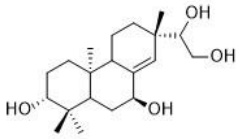

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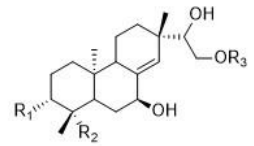
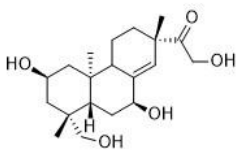


38 R_1 = OH, R_2 = CH_2OH, R_3 = H
39 R_1 = OGlc, R_2 = CH_3, R_3 = Ac



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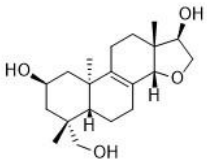

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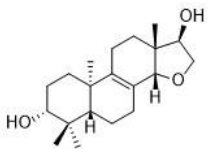

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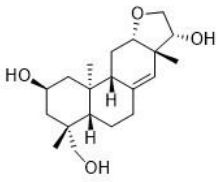

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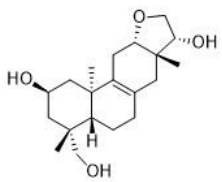

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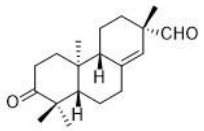

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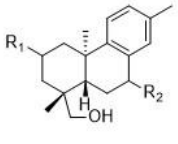
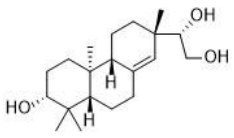


47 R_1 = O, R_2 =O
48 R_1 = β-OH, R_2 = H



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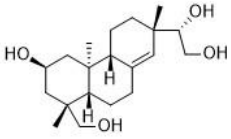

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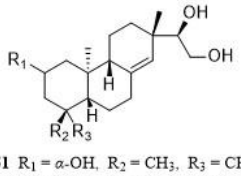
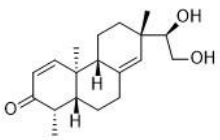


51 R_1 = α-OH, R_2 = CH_3, R_3 = CH_2OH
52 R_1 = β-OH, R_2 = CH_2OH, R_3 = CH_3



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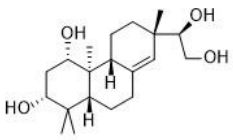

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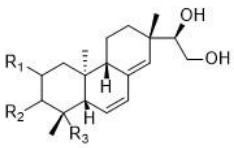
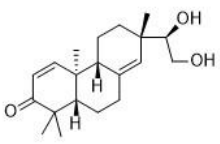


55 R_1 = H, R_2 = α-OH, R_3 = CH_3
56 R_1 = β-OH, R_2 = H, R_3 = CH_2OH



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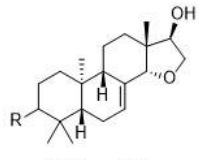
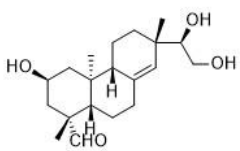


58 R = α-OH
59 R = β-OH



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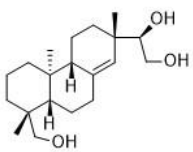

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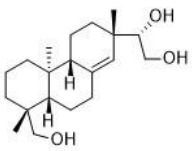

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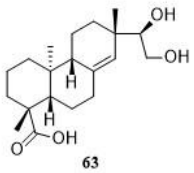

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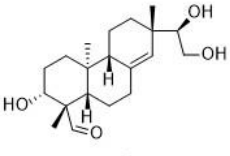

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(To be continued)

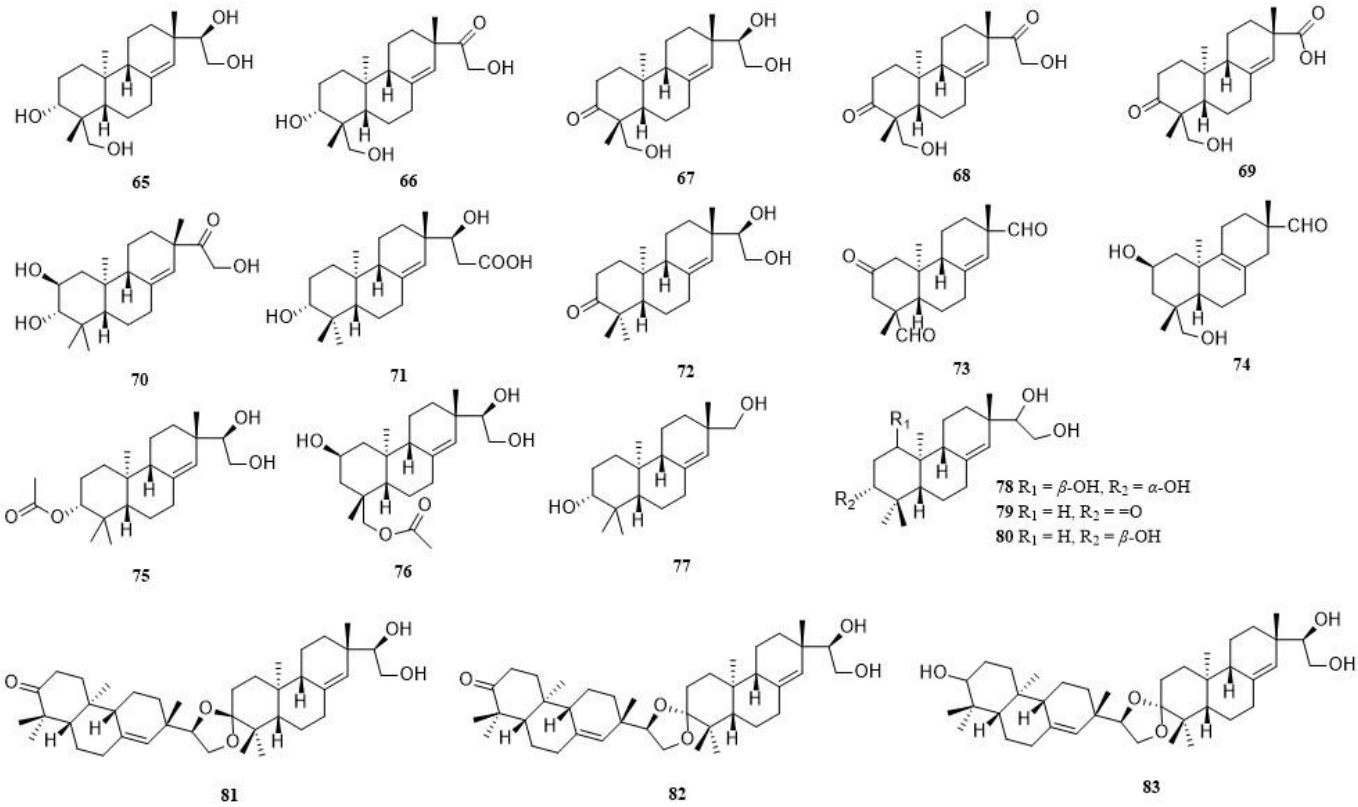

Figure 1. The structures of *ent*-pimarane diterpenoids (**1**-**83**) isolated from genus *Siegesbeckia*

Table 2. The structures of *ent*-kaurane diterpenes, chains, and *ent*-strobane diterpenoids isolated from genus *Siegesbeckia*

No.	Compounds	Plants	Ref.	No.	Compounds	Plants	Ref.
84	siegesbeckiol	*S. pubescens*	[22]	**107**	*ent*-16*α*H-kauran-17,19-dioic acid	*S. pubescens*	[14]
85	siegesbeckioside	*S. pubescens*	[22]	**108**	siegesmethyletheric acid	*S. orientalis*	[23]
86	siegesbeckic acid	*S. pubescens*	[22]	**109**	*ent*-16*β*H,17-isobutyryloxy-kauran-19-oic acid	*S. glabrescens*	[24]
87	*ent*-kauran-16*β*,17,18-triol	*S. pubescens*	[22]	**110**	grandifloric acid	*S. pubescens*	[22]
88	*ent*-l6*β*,17-dihydroxy-kauran-19-oic acid	*S. pubescens*	[22]	**111**	16*α*,17-acetonide of *ent*-19-methyl-16*α*,17-dihydroxykauran-19-oic acid	*S. pubescens*	[14]
89	*ent*-16*α*H,17-hydroxy-kauran-19-oic acid	*S. pubescens*	[22]	**112**	16*α*,17-acetonide of *ent*-19-methyl-16*R*,17-dihydroxykauran-19-oic acid	*S. pubescens*	[14]
90	*ent*-16*β*,17,18-trihydroxy-kauran-19-oic acid	*S. pubescens*	[25]	**113**	2-*O*-[*β*-D-apiofuranosyl-(1→3)-2-*O*-isovaleryl-*β*-D-glucopyranosyl]-4-epi-atractyligenin	*S. pubescens*	[26]
91	*ent*-16*β*,17-dihydroxy-kauran-19-oic acid	*S. pubescens*	[25]	**114**	2-*O*-[*β*-D-apiofuranosyl-(1→3)-2-*O*-(3-methylpentanoyl)-*β*-D-glucopyranosyl]-4-epi-atractyligenin	*S. pubescens*	[26]

Table 2 continued..

92	siegesesteric acid I	*S. orientalis*	[27]	**115**	2-*O*-[*β*-D-apiofuranosyl-(1→3)-2-*O*-isovaleryl-*β*-D-glucopyranosyl]atractyligenin	*S. pubescens*	[26]
93	siegesetheric acid II	*S. orientalis*	[27]	**116**	2-*O*-(2-*O*-isovaleryl-*β*-D-glucopyranosyl)-4-epi-atractyligenin	*S. pubescens*	[26]
94	*ent*-kauran-19*β*,17-diol	*S. glabrescens*	[28]	**117**	19-acetoxy-12-oxo-10,11-dihydrogeranylnerol	*S. orientalis*	[12]
95	16*α*H-siegesmethyletheric acid	*S. pubescens*	[28]	**118**	19-acetoxy-15-hydroperoxy-12-oxo-13,14*E*-dehydro-10,11,14,15-tetrahydrogeranylnerol	*S. orientalis*	[12]
96	*ent*-18-acetoxy-17-hydroxy-16*β*H-kauran-19-oic acid	*S. pubescens*	[14]	**119**	19-acetoxy-15-hydroxy-12-oxo-13,14*E*-dehydro-10,11,14,15-tetrahydrogeranylnerol	*S. orientalis*	[12]
97	*ent*-18-acetoxy-16*α*,17-dihydroxykauran-19-oic acid	*S. pubescens*	[14]	**120**	1,15,19-trihydroxygeranylnerol-2*Z*,6*Z*,10*E*,13*E*-tetraen-12-one	*S. pubescens*	[21]
98	*ent*-18-acetoxy-17-isobutyryloxy-16*β*H-kauran-19-oic acid	*S. pubescens*	[14]	**121**	19-acetyloxy-1,15-dihydroxygeranylnerol-2*Z*,6*Z*,10*E*,13*E*-tetraen-12-one	*S. pubescens*	[21]
99	*ent*-18-acetoxy-16*α*-hydroxy-17-isobutyryloxykauran-19-oic acid	*S. pubescens*	[14]	**122**	1,12,18,19-tetrahydroxyphyta-2*Z*,6*Z*,10*E*,14-tetraene	*S. orientalis*	[29]
100	*ent*-16R,17,18-trihydroxykauran-19-oic acid	*S. pubescens*	[14]	**123**	18-acetoxy-1,12,14,15,19-pentahydroxyphyta-2*Z*,6*Z*,10*E*-triene	*S. orientalis*	[29]
101	*ent*-17,18-dihydroxy-16H-kauran-19-oic acid	*S. pubescens*	[14]	**124**	12,15-epoxy-1,14,18,19-tetrahydroxyphyta-2*Z*,6*Z*,10*E*-triene	*S. orientalis*	[29]
102	*ent*-17-isobutyryloxy-18-hydroxykauran-19-oic acid	*S. pubescens*	[14]	**125**	18-acetoxy-1,2,3,12,19-pentahydroxy phyta-6*Z*,10*E*,14-triene	*S. orientalis*	[29]
103	*ent*-16*α*,17-dihydroxykauran-19-oic acid	*S. pubescens*	[14]	**126**	strobol A	*S. pubescens*	[10]
104	*ent*-17-hydroxy-16*α*H-kauran-19-oic acid	*S. pubescens*	[14]	**127**	strobol B	*S. pubescens*	
105	*ent*-19-methyl-17-hydroxy-16*α*H-kauran-19-oic acid	*S. pubescens*	[14]	**128**	17(13→14)-abeo-*ent*-3*S**,13*S**,16-trihydroxystrob-8(15)-ene	*S. orientalis*	
106	methyl ent-16*α*, 17-dihydroxy-kauran-19-oate	*S. glabrescens*	[31]				

2.2. Sesquitepenoids

Sesquiterpeneis the second most prevalent class of bioactive compounds (**129**-**199**) from genus *Siegesbeckia*. Germacranolide is the most common sesquiterpenoid among them, which contains an *α*-methylene-γ-lactonicring linked with a 10-carbon ring, often oxidized atC-8, C-9 C-14 or C-15 [32]. Wu et al. identified two sesquiterpenoids (**151**, **152**) with a bicycle[6.3.0]-γ-lactone structure in their skeleton [33]. The sesquiterpenoid (**155**) was identified with a rare 11(7→6)abeo-14-norcarabrane structure [34]. Besides, the compound (**195**) is a guaiane-type sesquiterpenoid from *S. pubescens* [21]. Recently, Hang et al. also isolated four undescribed guaianolide sesquiterpenesfrom the aerial parts of *S. orientalis*(**196**-**199**) [35].

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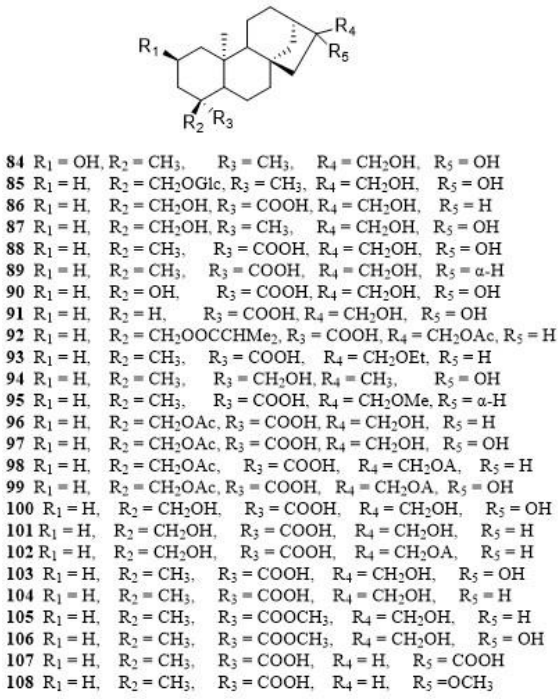
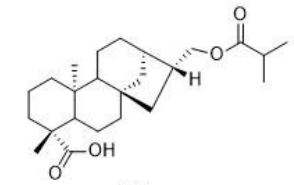


84 R_1 = OH, R_2 = CH_3, R_3 = CH_3, R_4 = CH_2OH, R_5 = OH
85 R_1 = H, R_2 = CH_2OGlc, R_3 = CH_3, R_4 = CH_2OH, R_5 = OH
86 R_1 = H, R_2 = CH_2OH, R_3 = COOH, R_4 = CH_2OH, R_5 = H
87 R_1 = H, R_2 = CH_2OH, R_3 = CH_3, R_4 = CH_2OH, R_5 = OH
88 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = CH_2OH, R_5 = OH
89 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = CH_2OH, R_5 = α-H
90 R_1 = H, R_2 = OH, R_3 = COOH, R_4 = CH_2OH, R_5 = OH
91 R_1 = H, R_2 = H, R_3 = COOH, R_4 = CH_2OH, R_5 = OH
92 R_1 = H, R_2 = $CH_2OOCCHMe_2$, R_3 = COOH, R_4 = CH_2OAc, R_5 = H
93 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = CH_2OEt, R_5 = H
94 R_1 = H, R_2 = CH_3, R_3 = CH_2OH, R_4 = CH_3, R_5 = OH
95 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = CH_2OMe, R_5 = α-H
96 R_1 = H, R_2 = CH_2OAc, R_3 = COOH, R_4 = CH_2OH, R_5 = H
97 R_1 = H, R_2 = CH_2OAc, R_3 = COOH, R_4 = CH_2OH, R_5 = OH
98 R_1 = H, R_2 = CH_2OAc, R_3 = COOH, R_4 = CH_2OA, R_5 = H
99 R_1 = H, R_2 = CH_2OAc, R_3 = COOH, R_4 = CH_2OA, R_5 = OH
100 R_1 = H, R_2 = CH_2OH, R_3 = COOH, R_4 = CH_2OH, R_5 = OH
101 R_1 = H, R_2 = CH_2OH, R_3 = COOH, R_4 = CH_2OH, R_5 = H
102 R_1 = H, R_2 = CH_2OH, R_3 = COOH, R_4 = CH_2OA, R_5 = H
103 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = CH_2OH, R_5 = OH
104 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = CH_2OH, R_5 = H
105 R_1 = H, R_2 = CH_3, R_3 = $COOCH_3$, R_4 = CH_2OH, R_5 = H
106 R_1 = H, R_2 = CH_3, R_3 = $COOCH_3$, R_4 = CH_2OH, R_5 = OH
107 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = H, R_5 = COOH
108 R_1 = H, R_2 = CH_3, R_3 = COOH, R_4 = H, R_5 = OCH_3



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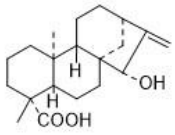

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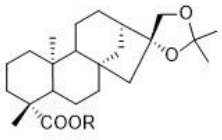
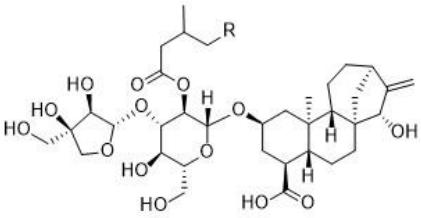
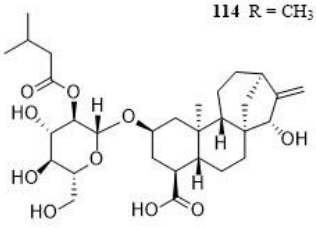


111 R=H
112 R=CH_3



113 R = H
114 R = CH_3



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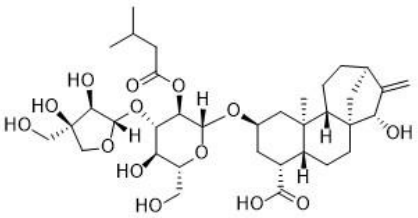

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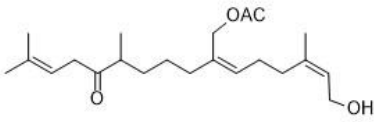

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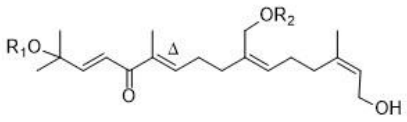
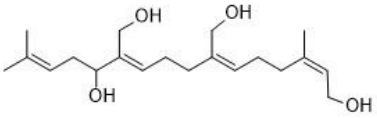


118 R_1 = OH, R_2 = Ac, Δ satd
119 R_1 = H, R_2 = Ac, Δ satd
120 R_1 = H, R_2 = H
121 R_1 = H, R_2 = Ac



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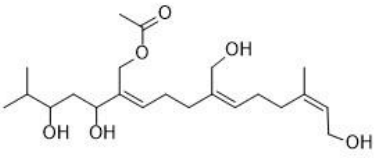

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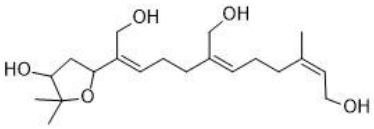

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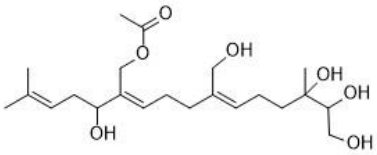

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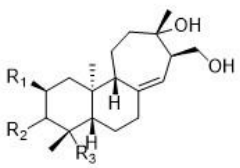
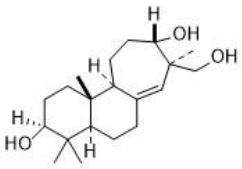


126 R_1 = β-OH, R_2 = H, R_3 = CH_2OH
127 R_1 = H, R_2 = α-OH, R_3 = CH_3



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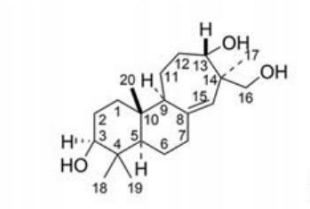


Figure 2 ane diterpenes (**84-116**), chains (**117-125**), and *ent*-strobane isolated from genus *Siegesbeckia*.

Table 3. The structures of sesquitepenes isolated from genus *Siegesbeckia*

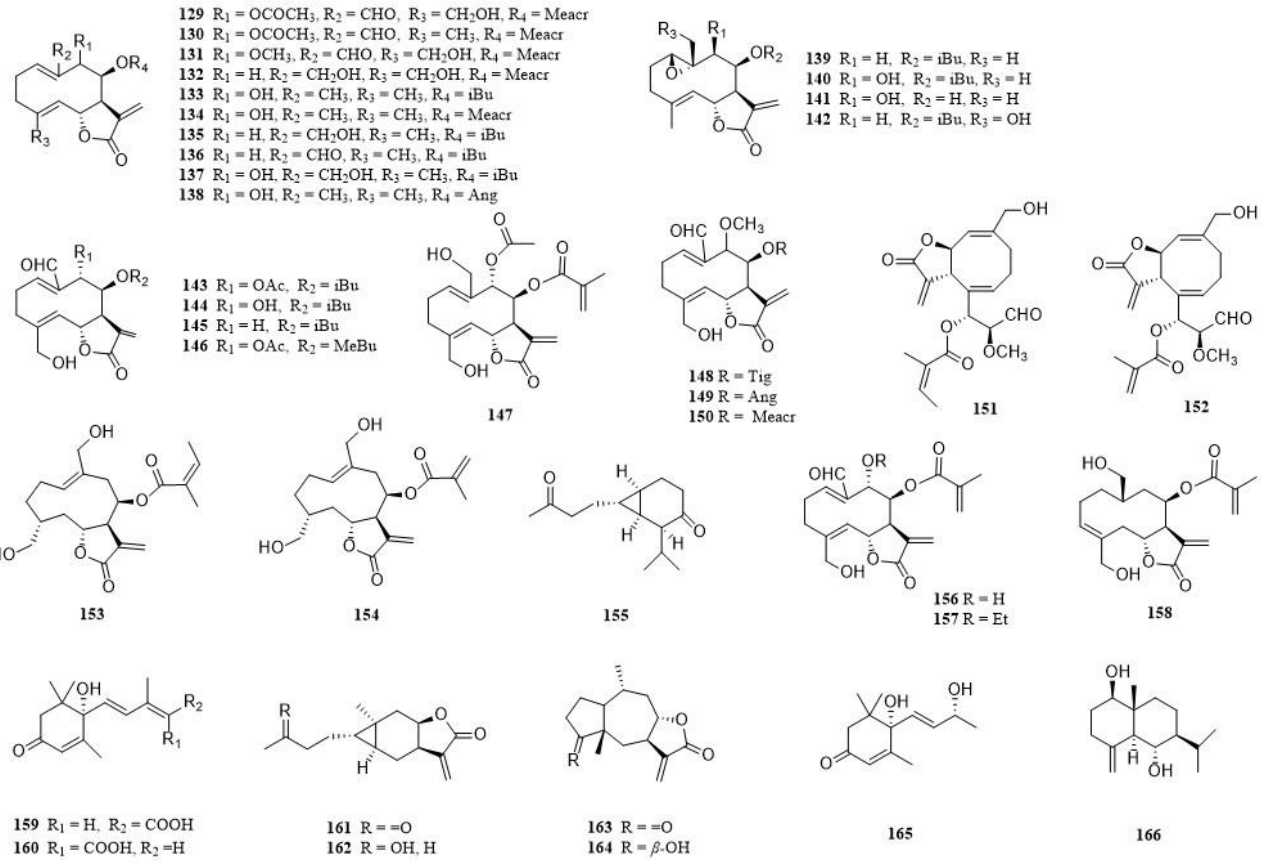
No.	Compounds	Plants	Ref.	No.	Compounds	Plants	Ref.
129	orientalide	*S. orientalis*	[36]	**165**	vomifoliol	*S. pubescens*	[34]
130	melampolide 1b	*S. orientalis*	[3]	**166**	(1*β*,6*α*)-eudesm-4(14)-ene-1,6-diol	*S. pubescens*	[34]
131	melampolide 4a	*S. orientalis*	[3]	**167**	(9*β*)-caryolane-1,9-diol	*S. pubescens*	[34]
132	orientin	*S. pubescens*	[28]	**168**	(10*α*)-hydroxyamorphan-4-en-3-one	*S. pubescens*	[34]
133	9*β*-hydroxy-8*β*-isobutyryloxycostunolide	*S. orientalis*	[12]	**169**	epiloliolide	*S. pubescens*	[13]
134	9*β*-hydroxy-8*β*-methacryloyloxycostunolide	*S. orientalis*	[12]	**170**	loliolide	*S. pubescens*	[13]
135	14-hydroxy-8*β*-isobutyryloxycostunolide	*S. orientalis*	[12]	**171**	dehydrovomifoliol	*S. pubescens*	[13]
136	8*β*-isobutyryloxy-14-al-costunolide	*S. orientalis*	[12]	**172**	(4*β*,10*E*)-6*α*,15-dihydroxy-8*β*-(isobutyryloxy)-14-oxogermacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
137	9*β*,14-dihydroxy-8*β*-isobutyryloxycostunolide	*S. orientalis*	[12]	**173**	(4*β*,10*E*)-6*α*,15-dihydroxy-8*β*-(methacryloxy)-14-oxogermacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
138	germacranolide	*S. orientalis*	[12]	**174**	(4*β*,10E)-6*α*,15-dihydroxy-8*β*-(angeloyloxy)-14-oxogermacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
139	8*β*-isobutyryloxy-1*β*,10*α*-epoxycostunolide	*S. orientalis*	[12]	**175**	(4*β*,10*E*)-6*α*,15-dihydroxy-8*β*-(tigloyloxy)-14-oxogermacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
140	9*β*-hydroxy-8*β*-isobutyryloxy-1*β*,10*α*-epoxycostunolide	*S. orientalis*	[12]	**176**	(4*β*,10E)-6*α*,15-dihydroxy-8*β*-(senecioyloxy)-14-oxogermacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
141	8*β*, 9*β*-dihydroxy-1*β*,10*α*-epoxy-11*β*,13-dihydrocostunolide	*S. orientalis*	[12]	**177**	(4*β*,10*E*)-6*α*,14,15-trihydroxy-8*β*-(tigloyloxy)-germacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
142	14-hydroxy-8*β*-isobutyryloxy-1*β*,10*α*-epoxycostunolide	*S. orientalis*	[12]	**178**	(4*β*,10*E*)-6*α*,14,15-trihydroxy-8*β*-(senecioyloxy)-germacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
143	15-hydroxy-9*α*-acetoxy-8*β*-isobutyryloxy-14-oxo-melampolide	*S. orientalis*	[12]	**179**	(1(10)*E*,4*Z*)-9*α*-ethoxy-6*α*,15-dihydroxy-8*β*-(tigloyloxy)-14-oxogermacra-1(10),4,11(13)-triene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
144	9*α*,15-dihydroxy-8*β*-isobutyryloxy-14-oxo-melampolide	*S. orientalis*	[12]	**180**	(1(10)*E*,4*Z*)-6*α*,9*α*,15-trihydroxy-8*β*-(tigloyloxy)-14-oxogermacra-1(10),4,11(13)-triene-12-oic acid 12,6-lactone	*S. orientalis*	[32]

Table 3 continued..

145	15-hydroxy-8*β*-isobutyryloxy-14-oxo-melampolide	*S. orientalis*	[12]	**181**	(1(10)*E*,4*Z*)-9*α*-acetyloxy-6*α*,14,15-trihydroxy-8*β*-(tigloyloxy)-germacra-1(10),4,11(13)-triene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
146	the melampolide	*S. orientalis*	[12]	**182**	(1(10)*E*,4*Z*)-6*α*,8*β*,15-trihydroxy-9*α*-(methacryloxy)-14-oxogermacra-1(10),4,11(13)-triene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
147	siegesbeckialide A	*S. pubescens*	[13]	**183**	(4*β*,10E)-6*α*,14,15-trihydroxy-8*β*-(isobutyryloxy)germacra-10,11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
148	siegesbeckialide B	*S. pubescens*	[13]	**184**	2-propenoic acid, 2-methyl-2,3,3a,4,5,8,9,10,11,11a decahydro-6,10-bis(hydroxymethyl)-3-methylene-2-oxocyclodeca[b] furan-4-yl ester	*S. orientalis*	[32]
149	4,11(13)-trien-12-oic acid 12,6-lactone	*S. pubescens*	[13]	**185**	(1(10)*E*,4*β*)-8*β*-(angeloyloxy)-6*α*,14,15-trihydroxygermacra-1(10),11(13)-diene-12-oic acid 12,6-lactone	*S. orientalis*	[32]
150	pubetalin	*S. pubescens*	[13]	**186**	9*α*-ethoxy-8*β*-(2-isobutyryloxy)-14-oxo-acanthospermolide	*S. orientalis*	[32]
151	siegenolide A	*S. glabrescens*	[33]	**187**	(2*Z*)-2-methylbut-2-enoic acid (3a*S*,4*S*,5*S*,6*E*,10*Z*,11a*R*)-5-(ethoxy)-6-formyl-2,3,3a,4,5,8,9,11a-octahydro-10-(hydroxymethyl)-3-methylene-2-oxocyclodeca[b]furan-4-yl ester	*S. orientalis*	[32]
152	siegenolide B	*S. glabrescens*	[33]	**188**	lecocarpinolide F	*S. orientalis*	[32]
153	2-methylbut-2-enoic acid,2,3,3a,4,5,8,9,10,11,11a-decahydro-6,10-bis(hydroxymethyl)-3-methylene-2-oxocyclodeca[b]furan-4-yl ester	*S. glabrescens*	[33]	**189**	(3a*S*,4*S*,5*S*,6*Z*,10*Z*,11a*R*)-5-(acetyloxy)-2,3,3a,4,5,8,9,11a-octahydro-6,10-bis(hydroxymethyl)-3-methylene-2-oxo-cyclodeca[b]furan-4-yl ester	*S. orientalis*	[32]
154	2-methylacrylic acid,2,3,3a,4,5,8,9,10,11,11a-decahydro-6,10-bis(hydroxymethyl)-3-methylene-2-oxocyclodeca[b]-furan-4-yl ester	*S. glabrescens*	[33]	**190**	lecocarpinolide B	*S. orientalis*	[32]
155	pubescone	*S. pubescens*	[34]	**191**	(6*R*,8*S*,9*S*)-9-ethoxy-6-hydroxy-8-methacryloxy-14-oxogermacra-1(10)*E*,4*E*,11(13)-triene-12,6-lactone	*S. pubescens*	[21]

Table 3 continued..

156	(1(10)*E*,4*Z*,6a,8b,9a)-6,9,15-trihydroxy-8-(2-methylacryloxy)-14-oxogermacra-1(10),4,11(13)-trieno-12,6-lactone	*S. pubescens*	[34]	**192**	8*β*-hydroxy-9*α*-methacryloyloxy-14-oxo-acanthospermolide	*S. pubescens*	[21]
157	(1(10)*E*,4*Z*,6*α*,8*β*,9*α*)-9-ethoxy-6,15-dihydroxy-8-(2-methylacryloxy)-14-oxogermacra-1(10),4,11(13)-trieno-12,6-lactone	*S. pubescens*	[34]	**193**	(6*R*,8*S*,9*S*)-9-acetyloxy-6,14-dihydroxy-8-methacryloxy-germacra-(10)*E*,4*Z*,11(13)-triene-12,6-lactone	*S. pubescens*	[21]
158	(3*E*,6*α*,8*β*)-6,14,15-trihydroxy-8-(2-methylacryloxy) germacra-3,11(13)-dieno-12,6-lactone	*S. pubescens*	[34]	**194**	8*R*-methylacryloxy-14-hydroxy-15-al-3(4),11(13)-germacradien-6,12-olide	*S. pubescens*	[21]
159	(*E*,*E*)-abscisic acid	*S. pubescens*	[34]	**195**	(4*R*, 6*R*, 8*S*)-4,6,15-trihydroxy-8-methacryloxy-14-oxoguaia-9*E*, 11(13)-diene-12, 6-lactone	*S. pubescens*	[21]
160	(*Z*,*E*)-abscisic acid	*S. pubescens*	[34]	**196**	siegesorienolide A	*S. orientalis*	[35]
161	carabrone	*S. pubescens*	[34]	**197**	siegesorienolide B	*S. orientalis*	[35]
162	4H-carabrone	*S. pubescens*	[34]	**198**	siegesorienolide C	*S. orientalis*	[35]
163	2,3-dihydroaromaticin	*S. pubescens*	[34]	**199**	siegesorienolide D	*S. orientalis*	[35]
164	2-deoxy-4-epipulchellin	*S. pubescens*	[34]				



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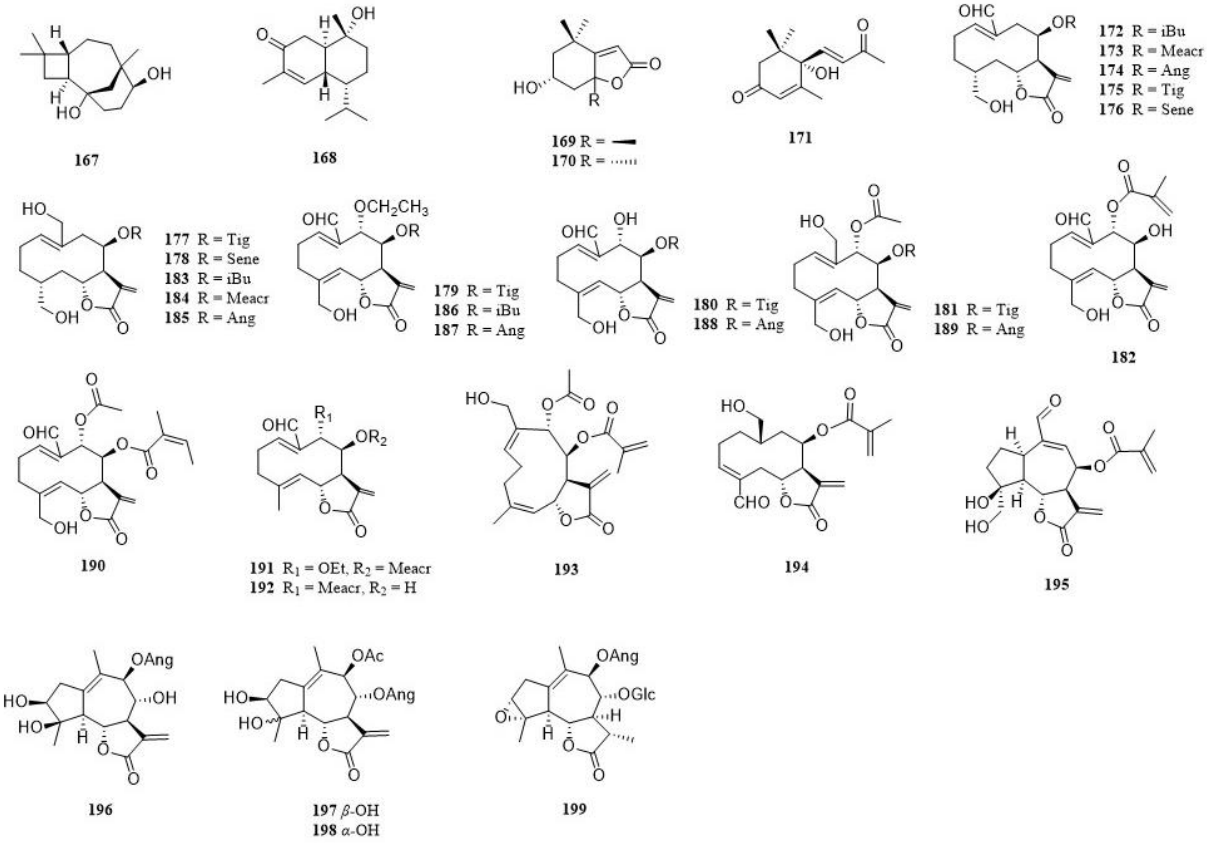


Figure 3. The structures of sesquitepenes (**129**-**199**) isolated from genus *Siegesbeckia*.

2.3. Flavonoids and Other Compounds

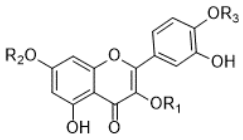
The content of flavonoids from *Siegesbeckia* species was relatively low compared with terpenes, and only 14 flavonoids were isolated and identified from genus *Siegesbeckia* (**200**-**213**). A total of 37 other types of compounds were also isolated from genus *Siegesbeckia*, including steroids, fatty acids and alcohols, phenylpropanoids, alkaloids and so on. It was worth to note that seven rare oxylipins (**233**-**239**) [37] and six new lignanoids (**240**-**245**) [38] with complex chemical structures were isolated from *S. glabrescens.*

Table 4. Flavonoids and other compounds isolated fromgenus *Siegesbeckia*

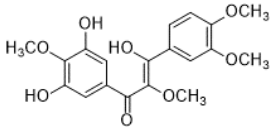
No.	Compounds	Plants	Ref.	No.	Compounds	Plants	Ref.
200	quercetin	*S. pubescens*	[39]	**226**	epoxyligan	*S. pubescens*	[39]
201	3,7-dimethylquercetin	*S. orientalis*	[8]	**227**	(E)-3-(3-oxobut-1-enyl)phenyl	*S. pubescens*	[40]
202	3,4′-*O*-dimethylquercetin	*S. glabrescens*	[41]	**228**	ursolic acid	*S. pubescens*	[42]
203	3-*O*-methylquercetin	*S. glabrescens*	[41]	**229**	N-(N-benzoyl-L-phenylalanine)-*O*-acetyl-L-phenylalanol	*S. pubescens*	[42]
204	3,7,4′-*O*-trimethylquercetin	*S. glabrescens*	[41]	**230**	tetracosa-carbonic acid	*S. pubescens*	[42]

Table 4 continued..

205	3′,5′,*β*-trihydroxy-3,4,4′, *α*-tetramethoxy-chalcone	*S. pubescens*	[43]	**231**	3-dodecanoyloxy-2-isobutyryloxy-4 -methylpentanoic	*S. glabrescens*	[44]
206	3,4-dimethoxy-2′,4′-dihydro xy chalcone	*S. glabrescens*	[45]	**232**	uracil	*S. orientalis*	[23]
207	7-*O*-(*β*-D-glucopyranosyl)-g alactin	*S. glabrescens*	[45]	**233**	siegesbeckin A	*S. glabrescens*	[37]
208	7,3′,4′-trihydroxy flavone	*S. glabrescens*	[45]	**234**	siegesbeckin B	*S. glabrescens*	[37]
209	5,6,7,3′,4′,5′-hexamethoxyfl avone	*S. glabrescens*	[45]	**235**	siegesbeckin C	*S. glabrescens*	[37]
210	8,3′,4′-trihydroxy-7-methox y flavanone	*S. glabrescens*	[45]	**236**	siegesbeckin D	*S. glabrescens*	[37]
211	5,4′-diyhydroxy-7,3′-dimeth oxy flavanone	*S. glabrescens*	[45]	**237**	siegesbeckin E	*S. glabrescens*	[37]
212	7,4′-dihydroxy-3′-methoxyfl avanone	*S. glabrescens*	[45]	**238**	siegesbeckin F	*S. glabrescens*	[37]
213	hesperidin	*S. pubescens*	[46]	**239**	siegesbeckin G	*S. glabrescens*	[37]
214	*β*-sitosterol	*S. orientalis*	[27]	**240**	glalignin A	*S. glabrescens*	[38]
215	*β*-sitosterol glucoside	*S. orientalis*	[27]	**241**	glalignin B	*S. glabrescens*	[38]
216	methyl arachidate	*S. orientalis*	[27]	**242**	glalignin C	*S. glabrescens*	[38]
217	heneicosanol	*S. orientalis*	[27]	**243**	glalignin D	*S. glabrescens*	[38]
218	glyceral monopalmitate	*S. glabrescens*	[47]	**244**	glalignin E	*S. glabrescens*	[38]
219	stigmasterol	*S. pubescens*	[48]	**245**	glaneolignin A	*S. glabrescens*	[38]
220	succinic acid	*S. pubescens*	[48]	**246**	(+)-isolariciresinol	*S. glabrescens*	[38]
221	ferulic acid	*S. pubescens*	[48]	**247**	(+)-syringaresinol	*S. glabrescens*	[38]
222	heptacosanol	*S. glabrescens*	[49]	**248**	dihydrodehydrodiconiferyl alcohol	*S. glabrescens*	[38]
223	syringic aldehyde	*S. pubescens*	[39]	**249**	tribulusamide A	*S. glabrescens*	[38]
224	D-mannitol	*S. pubescens*	[39]	**250**	chlorogenic acid	*S. pubescens*	[50]
225	2-amino-3-(3′-hydroxy-2′-m ethoxyphenyl)-1-propanol	*S. pubescens*	[39]				



200 R_1 = H, R_2 = H, R_3 = H
201 R_1 = CH_3, R_2 = CH_3, R_3 = H
202 R_1 = CH_3, R_2 = H, R_3 = CH_3
203 R_1 = CH_3, R_2 = H, R_3 = H
204 R_1 = CH_3, R_2 = CH_3, R_3 = CH_3



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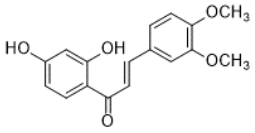

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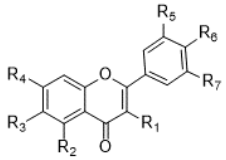
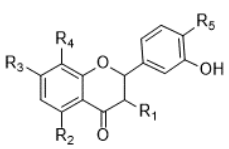
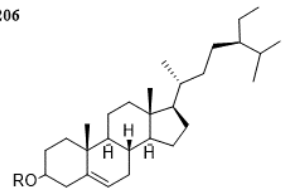


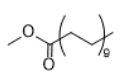
207 R_1 = OH, R_2 = OH, R_3 = OH, R_4 = OGlc, R_5 = H, R_6 = OH, R_7 = H
208 R_1 = H, R_2 = H, R_3 = H, R_4 = OH, R_5 = H, R_6 = OH, R_7 = OH
209 R_1 = H, R_2 = OCH_3, R_3 = OCH_3, R_4 = OCH_3, R_5 = OCH_3, R_6 = OCH_3, R_7 = OCH_3



210 R_1 = H, R_2 = H, R_3 = OCH_3, R_4 = OH, R_5 = OH
211 R_1 = OH, R_2 = OH, R_3 = OCH_3, R_4 = H, R_5 = OCH_3
212 R_1 = H, R_2 = H, R_3 = OH, R_4 = H, R_5 = OCH_3
213 R_1 = H, R_2 = OH, R_3 = OGlc-Rha, R_4 = H, R_5 = OCH_3



214 R = H
215 R = glc



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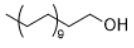

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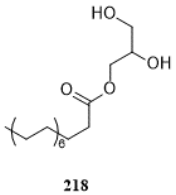

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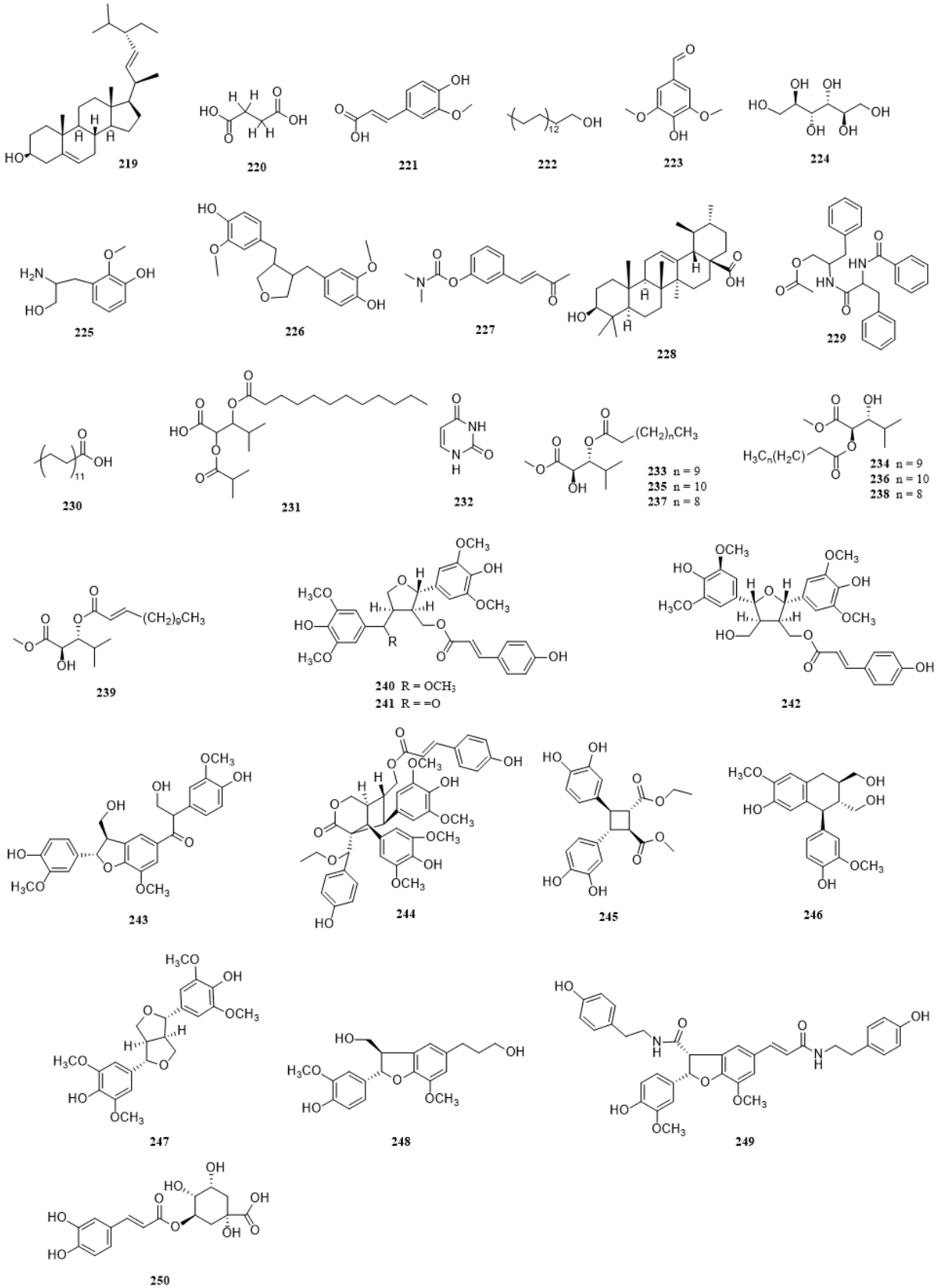

Figure 4. The flavonoids (**200-213**) and other compounds (**214-250**) isolated from genus *Siegesbeckia*

3. Pharmacological Activities

In recent years, more and more attention has been paid to *Siegesbeckia* species for prevention and treatment of diseases. Both the extracts and constituents of *Siegesbeckia* species have been investigated for their anti-thrombotic, anti-inflammatory, anti-allergic, immune-suppressive, anti-microbial, anti-oxidant and other therapeutic activities.

3.1. Anti-inflammation and Analgesia

Plants of genus *Siegesbeckia* has been used as a medicinal herb for treatment of various inflammatory diseases in ancient China. Hong and colleagues proved that the ethanol extract of *S. orientalis* possesses *in vitro* and *in vivo* anti-inflammatory effects via blocking the mitogen-activated protein kinases (MAPKs) and NF-κB pathways [51]. Meanwhile, *S. glabrescens* extract could attenuate the collagen-induced arthritis by the inhibition of synovial hyperplasia and inflammation via blocking NF-κB pathway [52]. Furthermore, Guo et al. further investigated the 50% ethanol extract of *S. orientalis* on the involvement of TLR4 signaling cascades on inflammatory mediators in murine macrophages. They found the extract inhibited inflammatory mediators regulated by AP-1, NF-κB and IRF3 [53]. In another study, *S. orientalis* extract was found to alleviate cartilage injury in rats with knee osteoarthritis, repair joint function and other clinical symptoms by upregulating sirt1 expression and downregulating FOXO1 acetylation level [54]. Moreover, the 50% ethanol extract of *S. pubescens* attenuated Pam_3CSK_4-induced inflammatory via inhibition of TLR 1/2-mediated NF-κB activation [55]. Additionally, Quan et al. developed a transdermal patch containing *S. pubescens* extract used for rheumatoid arthritis therapy. The new patch exhibited desirable anti-inflammatory and analgesic activity in chronic inflammation model [56].Besides, several reports showed the plants of genus *Siegesbeckia* also had potent neuroprotective activity. Akanda and co-workers reported the neuroprotective effect of *S. pubescens* on glutamated-induced oxidative stress in HT22 cells, and found that *S. pubescens* downregulated MAPK/caspase-3 pathway [57]. In addition, *S. orientalis* also showed attenuation of systemic and neuroinflammation, as well as cognitive dysfunction in postoperative experimental animals [58].

Comparing with three common *Siegesbeckia* herbs, *S. pubescens*, *S. orientalis* and *S. glabrescens* for the inhibitory effect on nitric oxide (NO) production and IL-6 expression in lipopolysaccharide (LPS)-induced RAW264.7 cells, *S. glabrescens* showed the most potent among them [59]. In addition, Zhong et al. conducted an *in vitro* and in silico investigation, proving that *S. glabrescens* exerted significant anti-inflammation in LPS-stimulated RAW264.7 cells by inactivation of NF-κB without influencing MAPK pathway [60]. Recently, Linghu and co-workers conducted a comparison in the anti-inflammatory effect of three *Siegesbeckia* herbs, and *S. glabrescens* was weaker than the other two herbs but similar inhibitory activity on NF-κB and MAPKs signaling of three herbs were observed [61]. As for essential oils from different *Siegesbeckia* plants, Gao et al. proved that the essential oil of *S. pubescens* could reduce the NO production of LPS-induced RAW264.7 cells, and that of *S. orientalis* significantly reduced the release of cytokine IL-6 [62].

Kirenol (**6**), a main *ent*-pimarane diterpenoid in genus *Siegesbeckia* plants, is considered as one of the main anti-inflammatory constituents. Recently, Ibrahim et al. provided a detailed review on the pharmacological activities of kirenol [63]. The anti-inflammatory effect of kirenol at concentration of 0.4~0.5% was comparable with piroxicam gel in a carrageenan-induced rat acute inflammation model [64]. Compared with prednisolone, kirenol did not lead to adrenal corticotropin or glucocorticoids receptor downregulation [65]. The effect might be owing to reduction of the expression of IL-1 and TNF-α [64], suppression of some essential markers like iNOS and COX-2 [66], upregulation of nuclear Annexin-1 to inhibit NF-κB pathway [65]. Furthermore, Wu et al. found kirenol suppressed the migration of rheumatoid arthritis-associated synovial fibroblasts and IL-6 expression. It also inhibited proinflammatory cytokines secretion, synovium hyperplasia in arthritis mouse models [67]. Additionally, kirenol showed desirable wound management in hyperglycemic mouse models through suppression anti-inflammatory NF-κB pathways, which made it potential for dealing unceasing lesions of diabetic patients [66].

In addition to kirenol, another diterpene, *ent*-16αH,17-hydroxy-kauran-19-oic acid (**89**) also showed favorable anti-inflammatory and anti-nociceptive compound by activity-guided extraction. The mechanism was considered to be associated with inactivating NF-κB binding capability [68]. Similarly, activity-guided extraction afforded a series of *ent*-kaurane diterpenoids and kirenol from 90% methanol fraction of *S. pubescens*. Amongst, kirenol markedly inhibited LPS-induced NO release in BV2 microglia, and *ent*-16αH,17-hydroxy-kauran-19-oic acid and kirenol dose-dependently suppressed the expression of iNOs and COX-2 [69]. Recently, Gao et al. obtained nine new *ent*-pimarane-type diterpenoids and some of them (**62**, **66**, **68**) exhibited comparable inhibitory effect of NO release in LPS-stimulated BV2 microglia [15]. Furthermore, three new *ent*-pimarane diterpenoid dimers were identified from *S. glabrescens*.Amongst, glabreside C (**83**) dose-dependently promoted the production of heme oxygenase-1 (HO-1), suppressed iNOS and COX2 in LPS-exposed BV2 cells [2].

Apart from the studies on anti-inflammatory diterpenoids of *Siegesbeckia*, which are the major compounds from the herbs [69], latest studies demonstrated that sesquiterpenoids and flavonoids also showedanti-inflammatory activity. Wang and co-workers investigated the anti-inflammatory activity of a series of sesquiterpenoids and diterpenoids from *S. pubescens* Sesquiterpenoids showed more potent in inhibiting NO production than tested diterpenoids [70]. Furthermore, Li and colleagues analyzed the anti-inflammatory mechanism of a sesquiterpenoid lactone (**184**). It downregulated the expression of iNOS and COX-2 through inhibition of NF-κB pathway in LPS-stimulated macrophages [71]. Additionally, Engels et al. found a new bioactive sesquiterpene lactone (**128**) from *S. orientalis* with promising anti-inflammatory activity [30].Moreover, a flavonoid (**204**) from *S. pubescens* showed anti-neuroinflammatory effect as well. It markedly suppressed the oxidative stress of glutamate-induced cell damage via activating HO-1 in HT22 cells [1]. Besides, Lim reported four quercetin derivatives from *S. glabrescens* for treatment of neuro-inflammatory diseases, namely 3,7-dimethylquercetin (**201**), 3,4′-*O*-dimethylquercetin (**202**), 3-*O*-methylquercetin (**203**), 3,7,4′-*O*-trimethylquercetin (**204**). The flavonoids dose-dependently suppressed PGE_2 release and COX-2 in LPS-induced microglia [72]. Also, 3,7-dimethylquercetin (**201**) could suppress NO release and iNOS protein production in rodent macrophages by inhibition of IL-6, IL-1β, TNF-α. Besides, this flavonoid inhibited iNOS, COX-2 and IL-8 in HT-29 cells, which indicated that compound it might be promising for treatment of inflammatory bowel disease [73].Recently, hesperidin (**213**), together with kirenol and darutoside (**18**), was found to suppress the nociceptive stimulus-activated inflammatory infiltrates and the expression of COX-2 [46].

3.2. Antibacterial Activity

Genus *Siegesbeckia* has been proved to be a valuable source of natural anti-microbial products.Kim and co-workers investigated the anti-bacterial compounds from the *S. glabrescens* extract, from which 3-dodecanoyloxy-2-isobutyryloxy-4-methylpentanoic acid (**231**) was identified with minimal inhibitory concentration (MIC) of 3.12 μg/mL against *Staphylococcus aureus* [44]. Besides, kaurene diterpenoids (**88, 98, 99, 101**) from *S. orientalis* also exhibited striking anti-microbial activity against methicillin-resistant *Staphylococcus aureus* [23]. In addition, Wu and colleagues reported that rare oxylipins, siegesbeckin A (**233**) and siegesbeckin E (**237**) exhibited moderate anti-bacterial activity against gram-positive strains [37].

3.3. Antiallergic Activity

The elevated release of immunoglobulin E (IgE) was found to be related to immediate allergic reactions. Hwang et al. found that the water extract from *S. orientalis* could exert inhibitory effect on the interleukin (IL)-4-related IgE production in whole spleen cells and U266B1 cells. Furthermore, *S. orientalis* also suppressed the formation of IgE induced by LPS or LPS plus IL-4 [74]. Similarly, the water extract of *S. glabrescens* showed inhibitory effect on IgE production in rodents, which was related to the inhibition of systemic anaphylaxis and serum IgE [75]. Moreover, oral administration of *S. glabrescens* exhibited strong anti-allergic capacity via suppression of histamine production in mast cells [76].

3.4. Antiplatelet and antithrombotic Activity

The kaurene diterpenoid, *ent*-16,17-dihydroxy-kauran-19-oic acid (**88**), is an anti-thrombotic component extracted from *S. pubescens* which was known to exhibit vasodilating activity, hypotensive effect and alleviate the weight of thrombus [77]. Another study showed that it had anti-thrombotic effect and significantly reduced blood viscosity, promoted circulation and suppressed blood stasis [78].Furthermore, the anti-platelet and anti-thrombotic effects of this diterpenoid (**88**) were investigated by Wang et al. The mechanism was related with the anti-coagulatory effect and cAMP induction. In arterio-venous shunt model, it decreased thrombus weight and increased plasma cAMP level [79].

3.5. Anticancer Activity

Some compounds isolated from plants of genus *Siegesbeckia* showed potent anti-cancer activity. The sesquiterpene lactone (**154**), isolated from *S. glabrescens*, showed great potential as an inhibitor of the transcription factor glioma-associated oncogene (Gli) mediated transcription. Gli has been proved to play an essential role in Hedgehog signaling pathway, which is closely related with the proliferation of pancreatic cancer cells. This sesquiterpenoidcould inhibit Gli homolog 1-mediated transcriptional activity in mesen-chymal C3H10T1/2 stem cells [80]. Meanwhile, kirenol have also shown considerable cytotoxic activities against various cancer cells. Liu found that kirenol significantly decreased the incidence as well as the growth of gastric tumor via a significant suppression of lipid peroxidation [81]. Besides，the broad-spectrum anti-cancer activity of *S. glabrescens*extract has also been proved against breast cancer, ovarian cancer, non-small cell lung cancer cell lines [82]. The aqueous extract of *S. pubescens* could inhibited the proliferation of breast carcinoma cells through two pathways, including the intrinsic signal in MCF-7 cells and the extrinsic signal in MDA-MB-231 cells [83].

3.6. Immunosuppressive Activity

The ethanol extract of *S. orientalis* could inhibited immunoreaction induced by ovalbumin in mice. It dose-dependently inhibited concanavalin A (Con A)- and LPS-induced splenocyte *in vitro* proliferation with the reduction of IgG, IgG1, and IgG2b levels. Notably, compared with cyclosporin A, *S. orientalis* extract exhibited stronger reducing activity in IgG1 [84].Furthermore, Xiao et al. investigated the effects of kirenol on experimental autoimmune encephalomyelitis. The treatment with kirenol improved condition through suppressing Th1/Th17 cell differentiation and promoting apoptosis of MOG-specific CD4+ T cells via a mitochondrial pathway [85]. Moreover, kirenol showed its potential anti-arthritis capactiy in mice on the modulation of T cells [86].

3.7. Other Activities

The extract from genus *Siegesbeckia* were reported to be effective in epidermal regeneration and skin damage. Sung and co-workers investigated the epidermal regenerative potential of *ent*-16*α*,17-dihydroxykauran-19-oic acid (**103**) from *S. pubescens* using KSC cells. The compound stimulated KSC cells and increased the proliferation and migration through Akt ⁄ERK pathway, accelerating the heal of epidermal wounds [87]. Furthermore, Kim et al. evaluated the anti-photoaging effects of *S. glabrescens* extract and kirenol in mice. Both the water extract of aerial parts from *S. glabrescens* and kirenol upregulated the mRNA levels related with collagen synthesis genes, while downregulated matrix metalloproteinase (MMP) expression [88]. Recently, Shim et al. demonstrated *S. glabrescens*contains anti-melanogenesis compounds, such as kirenol and methyl ent-16α, 17-dihydroxy-kauran-19-oate (**106**), for prevention of oxidation-induced hyperpigmentation [31]. Moreover, airborne particulate matter (PM10) may cause oxidative damages and inflammation in skin. It was found that *S. pubescens* extract increased the cellular antioxidant capacity by activation of defense genes, mitigation of oxidative stress and also enhancement of cell survival rate under

PM10-based environment. This study also indicated that chlorogenic acid (**250**) might be one of the active ingredients with antioxidant and cytoprotective effects [50].

As for hepato-protection, Sun and colleagues investigated the activity of kirenol both *in vivo* and *in vitro*. Results showed that kirenol inhibited ROS level in HepG2 cells. Furthermore, kirenol exhibited powerful *in vivo* antioxidant and anti-inflammatory abilities via reducing uric acid, inhibiting lipid peroxidation as well as ameliorating liver tissue abnormality in rats [89].

Several researchers provided the scientific evidence for plants of genus *Siegesbeckia* could be helpful in protecting the body against endocrine disorders like obesity. The methanol extracts of *S. pubescens* was found to possess anti-oxidative and anti-obesity capacities. It exhibited DPPH radical scavenging effect with an IC_{50} value of 47.79 μg/mL. The anti-obesity activity was regulated via cytidine-cytidine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding proteins α (C/EBPα), C/EBPβ, and peroxisome proliferator-activated receptor (PPAR) gene and proteins expression [90]. Recently, Kim and co-workers found the high hydrostatic pressure extract of *S. orientalis* also showed anti-adipogenic activity, which was associated with the promotion of Wnt/β-catenin pathway [91]. Moreover, Kim et al. proved that kirenol could suppress intracellular lipid accumulation through downregulating C/EBPα, PPARγ, lipid-synthesis enzymes and adipocytokines. It also activated the Wnt/β-catenin signaling by increasing the expression of low density lipoprotein receptor related protein 6 (LRP6) and inactivating glycogen synthase kinase 3β (GSK3β) [92]. Besides, an activity-guided extraction provided two diterpeneswith potential anti-obesity effect, *ent*-16*β*H,17-isobutyryloxy-kauran-19-oic acid(**109**) and siegesesteric acid I (**92**). They were found to be non-competitive inhibitors of PTP1B [24].

As for fracture healing,Kim and colleagues investigated the activity of kirenol on treating or preventing osteoporosis. Results showed that it could enhance osteoblast differentiation of MC3T3-E1 cells through stimulating BMP expression and activating Wnt/β-catenin signaling pathways [93]. Furthermore, the treatment of kirenol enhanced a concentration-dependent acceleration of fracture healing, which was associated with the promotion of Wnt/β-catenin and Runx-2 pathways [94]. In an *in vivo* study, kirenol inhibited osteoclastogenesis and bone-resorption through suppression of Cav-1/NFATc1 and NF-κB/MAPKs/c-Fos pathways [95]. Moreover, a recent study showed that sesquiterpenoids from *S. pubescens* (**185**, **191**, **194**) exhibited potential inhibitory effect against RANKL-induced osteoclast formation with IC_{50} value of less than 1.0 μM, respectively [21].

Besides, the extracts or constituents of genus *Siegesbeckia* were also proved to be active in treatment of diabetes.The ethanol extract of *S. orientalis* showed protective effect in pancreatic β-cells under glucotoxic environment. The treatment of *S. orientalis* extract significantly downregulated the formulation of ROS, upregulated the level of glutathione and antioxidant enzymes [96].

4. Conclusion

Genus *Siegesbeckia* has been utilizedfor treatment of various diseases for hundreds of years in east Asia with desirable therapeutic effects. There is growing interest in exploring active compounds or extracts from genus *Siegesbeckia* in recent years. The modern pharmacological researches revealed the underlying mechanism of the traditional uses of *Siegesbeckia* and afforded some promising lead compounds like kirenol and several terpenoids. The potential for the development of new drugs from genus *Siegesbeckia* continues to grow, particularly in the field ofanti-inflammation and analgesia. However, there still remains quite a few problems. Most studies were limited to *in vitro* pharmacological experiments so far. The *in vivo* tests and clinical studies are still scarce for further confirmation of the therapeutic effects. Furthermore, the structure-activity relationship of compounds from genus *Siegesbeckia* should be paid more attention, which is essential for finding potential new therapeutic agent.Depending on the available literature, the potential therapeutic activities of different kinds of compoundscan be categorized generally, such as diterpenoids with anti-inflammatory, anti-cancer, anti-platelet activities and so on, sesquiterpenoids with anti-inflammatory and anti-cancer activities, flavonoids with anti-inflammatory activity. Nevertheless, there are still few reports on more specific structure-activity relationship based on single active compound and its analogues. Moreover, the interaction between bioactive compounds and extracts of genus *Siegesbeckia* with other herbs was

not studied in detail, although *Siegesbeckia* is usually used accompanied with many other herbs as anintegrated recipe. Besides, the *in vitro* and *in vivo* toxicity profiles of compounds or extracts from genus *Siegesbeckia* should be also investigated. The toxicity profiles of genus *Siegesbeckia* should be further studied for its applications in clinics practice, especially when it is utilized as a long-term drug for chronic diseases. Overall, there is a bright future for the clinical application of genus *Siegesbeckia*.

Author Contributions

Wang Dexia conceptualized the review and completed the initial version of the manuscript. Dong Xin and Nie Yanyan help with database search for the literature. Yang Wenting and Li Chengshou contributed in gathering of information and revision of the manuscript. All authors read and approved the final manuscript.

Funding: This work is supported by Qingdao Science and Technology Project of Traditional Chinese Medicine (No. 2021-zyyq05).

Conflicts of Interest: The authors declare no conflict of interest.

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